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Combination Therapy with Olmesartan/Hydrochlorothiazide to Improve Blood Pressure Control

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Abstract

Poor blood pressure (BP) control is a serious clinical problem, being responsible for much of the morbidity and mortality associated with arterial hypertension. Although European Society of Hypertension (ESH)/European Society of Cardiology (ESC) Guidelines for the management of arterial hypertension strongly recommend to pursue the primary therapeutic goal of BP control in the population of hypertensive patients, currently available data indicate that, in the western world, a large proportion of hypertensive patients have poor BP control. Relevant causes of poor BP control are clinical inertia, defined as failure of physicians to modify or intensify treatment of patients who do not achieve BP targets, and low patient adherence to the treatment. Improved BP control can be achieved by using appropriate antihypertensive drugs at adequate dosage and/or improving patients' adherence rate.

In the majority of hypertensive patients, a combination of two or more antihypertensive drugs is nearly always necessary in order to achieve adequate BP control as recommended by current ESH/ESC Guidelines. In such cases, the use of fixed-dose combinations can significantly improve patient adherence, through the reduction of daily “pill-burden”.

Olmesartan medoxomil (OM) is an antihypertensive agent belonging to the angiotensin II receptor antagonist (ARB) class which, in several clinical studies, has proved to be effective and well tolerated in the treatment of hypertensive patients. In patients in whom olmesartan medoxomil monotherapy fails to achieve the recommended BP goal, the combination of olmesartan medoxomil with the thiazide diuretic hydrochlorothiazide (HCTZ) can enhance the efficacy of the antihypertensive treatment (compared with placebo and monotherapy with either agent), thereby allowing a greater number of patients to achieve BP control.

Combination therapy with OM/HCTZ has shown good efficacy and a favorable tolerability profile in a number of clinical trials. In this review, we will examine the evidence in the literature on this subject and advance suggestions on the most rational way to use this therapy in clinical practice.

Keywords: Adherence; Blood pressure control; Combination therapy; Hydrochlorothiazide; Hypertension; Olmesartan medoxomil

Introduction

High blood pressure (BP) is a major risk factor for cardiovascular disease, contributing to the premature death of millions of patients worldwide each year [1]. In the most recent 2013 Guidelines of the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) for the management of arterial hypertension, high blood pressure is defined, based on results of randomized controlled trials (RCTs), as a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg [1]. According to recent epidemiological surveys, the overall prevalence of hypertension in the general population ranges from 30 to 45%, and increases markedly with age.

Increased mean BP values correlate with the development of cardiovascular disease (CVD) morbidity/mortality in a linear relationship; consequently, the greater the reduction in blood pressure, the greater the reduction in the risk [2]. ESC/ESH Guidelines point out that the initial choice of antihypertensive medication should be based on the magnitude of BP elevation, as well as on the concomitant level of total cardiovascular (CV) risk [1].

Despite the availability of very effective antihypertensive drug therapies, BP control in hypertensive patients remains largely unsatisfactory. This discrepancy between expected and actual outcomes may result from clinical inertia, defined as a failure of physicians to modify or intensify therapy when BP goals recommended by ESC/ESH Guidelines are not met, or from poor patient compliance to treatment regimen [3].

Uncontrolled hypertension is associated with a significant increase in CVD-related morbidity and mortality, as well as with the development of renal impairment/failure [1]. There is a wide evidence that BP control (<140/90 mmHg in patients without diabetes/renal disease, and <130/80 mmHg for those with diabetes/renal disease) can exert positive effects by significantly reducing the risk of stroke, heart failure, ischemic heart disease, and chronic kidney disease.

However, epidemiological studies performed in different Countries demonstrate that hypertension is still largely undertreated, and the reasons behind this poor control are multiple. Among these reasons, there are advanced patient age and poor patient adherence; also, one should not overlook the impact of socio-economic factors, and the

importance of physicians' familiarity with ESC/ESH treatment Guidelines, which are continually updated [3-5]. Indeed, treatment adherence is a key factor for the success of preventive interventions aimed at reducing the degree of CV risk [5]. The use of fixed-dose combination therapies can contribute significantly to the ambitious goal of filling the existing gap between recommended BP goals and real-life hypertension control in clinical practice, as suggested by the results of recent clinical trials. For example, in the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) Trial, the use of combination therapy as an initial strategy for the treatment of hypertension resulted in a very high percentage, close to 80%, of patients achieving well-controlled BP levels [4].

Patients (n) randomized to anti-hypertensive treatment	Male/Female (n)	Dosage (daily)	Baseline seated BP (mmHg)	Seated SBP/ Seated DBP reduction (mmHg)	% achieved BP target	Study Reference
					SeSBP<140 mmHg	[6]
		Placebo	152.1/103.4	3.3/8.2	33.3	
		OM 40 mg	152.9/102.6	16.0/14.6	60	
		HCTZ 25 mg	155.9/104.4	17.1/12.9	67.4	
502	280/222	OM/HCTZ 40/25 mg	153.6/103.4	26.8/21.9	87.2	
		OM/HCTZ 20/12.5 mg	155.8/97.2	11.6/8.0		[7]
		OM/HCTZ 20/25 mg	153.3/96.8	17.2/10.5		
		OM/HCTZ 40/12.5 mg	154.1/97.6	13.9/9.2		
1870	1143/727	OM/HCTZ 40/25 mg	153.9/97.3	17.3/11.2	NE	
					SeBP<140/90 mmHg	[9]
		Placebo	155.3/93.7	0.1/+0.8	30.7	
278	63/74	OM/HCTZ 40/25 mg	156.9/94.2	22.3/12.1	74.1	
		Benazepril/ amlodipine			SeBP<140/90 mmHg	[11]
		20/10 mg	169.6/101.4	26.5/N.R.	44.7	
191	102/89	OM/HCTZ 40/25 mg	167.0/101.7	32.5/N.R.	66.3	
					SeBP<140/90 mmHg (<130/80 mmHg for T2DM)	[12]
972	599/373	OM/HCTZ 40/25 mg	155.4/98.0	30.3/19.0	42.1	
					SeBP<140/90 mmHg	[14]
176	92/84	OM/HCTZ 40/25 mg	165.5/87.7	25.4/10.5	67	

Table 1: Antihypertensive efficacy of OM/HCTZ combination therapy: data from most relevant trials reviewed (6,7,9,11,12,14). BP: Blood Pressure; DBP: Diastolic Blood Pressure; HCTZ: Hydrochlorothiazide; NE: Not Evaluated; NR: Not Reported; OM, Olmesartan Medoxomil; SBP: Systolic Blood Pressure; T2DM: Type 2 Diabetes Mellitus.

As pointed out by 2013 ESH/ESC Guidelines, most hypertensive patients require combination therapy in order to achieve the recommended BP goals (140/90 mmHg for the general hypertensive population, and <140/80-85 mmHg for hypertensive patients with high-risk conditions, such as diabetes or renal disease).

However, there are still some unresolved issues, such as those concerning the initial therapeutic approach in hypertensive patients and, in particular, whether patients should be started on monotherapy or combination therapy. According to 2013 ESH/ESC Guidelines, the most obvious advantage of initiating treatment with monotherapy is that of using a single agent, thus being able to ascribe effectiveness and adverse effects to that agent. On the other hand, the disadvantage of monotherapy is that a single agent is often unable to achieve an adequate BP control, leading to several changes in dosages and/or medications.

A meta-analysis of more than 40 studies has shown that combining two antihypertensive agents has greater BP-lowering efficacy than increasing the dose of one agent [1]. Again, as emphasized by 2013 ESH/ESC Guidelines, the main advantage of initiating with combination therapy is a prompter response in a larger number of patients (potentially beneficial in high-risk patients), a greater probability of achieving the target BP in patients with higher BP values, and a better patients' adherence resulting in less treatment changes; additionally, patients receiving combination therapy have a lower discontinuation rate than patients given any monotherapy. There is also increasing evidence of physiological and pharmacological synergies between different classes of agents that enhance BP-lowering efficacy, improve treatment tolerability and may provide larger benefits than those offered by a single agent [1]. 2013 ESH/ESC Guidelines recommend the use of combination therapy as first therapeutic step in high-risk patients, or in those with very high BP values [1].

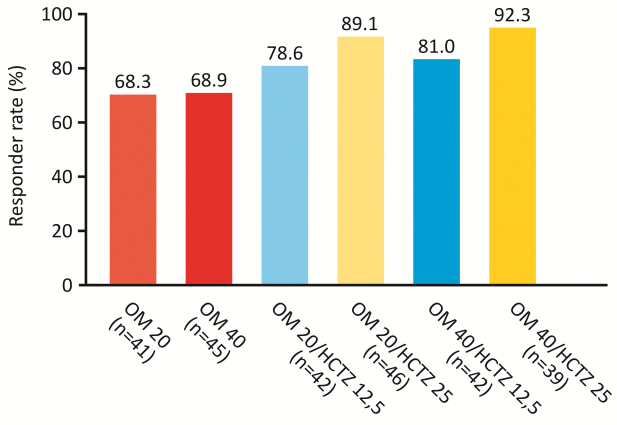


Figure 1: Responder rates (SeDBP<90 mmHg or 10 mmHg reduction in SeDBP) in groups treated with olmesartan (OM) and olmesartan medoxomil/hydrochlorothiazide (OM/HCTZ). Responder rates increase after switching from OM to OM/HCTZ, progressively increasing with up-titration of OM/HCTZ. Elaborated from (6).

A 'good' combination therapy involves the combined use of drugs with different but complementary modes of action, leading to an additive or even synergistic BP-lowering effect [1]. The benefits of drugs acting on RAS have been demonstrated in a variety of clinical conditions and settings, from asymptomatic patients with heart disease to patients with severe refractory heart failure and end-stage renal disease. It should also be remembered that RAS-blocking agents have proven beneficial effects in terms of reducing cardiovascular morbidity and mortality. The results of studies where RAS-blocking agents were associated with other classes of antihypertensive drugs, including thiazide diuretics, suggest that the implementation of fixed-dose combination strategies, based on agents that can inhibit the effects of abnormal RAS activation, may improve BP control and treatment tolerability [1].

In this review, we will examine the currently available evidence in the literature on combination therapy with olmesartan (OM), an angiotensin II receptor antagonist (ARB), and hydrochlorothiazide (HCTZ), a thiazide diuretic that can enhance the efficacy of the antihypertensive treatment.

Rationale of use and therapeutic effects of olmesartan/hydrochlorothiazide (OM/HCTZ) combination

According to the latest ESC/ESH Guidelines on hypertension management, one of the recommended combination therapies is the combination of an angiotensin receptor antagonist (ARB) with a thiazide diuretic. The rationale of this association is related not only to an increased BP-lowering efficacy, due to the synergistic and additive antihypertensive effects of the 2 agents, but also to the favorable impact on several pathophysiological mechanisms of hypertension, including the inhibition of counter-regulatory mechanisms activated by diuretics. Diuretics promote renal excretion of sodium and induce reflex activation of the renin-angiotensin system (RAS) via intrarenal mechanisms; such reflex activation makes BP more dependent on the RAS, thereby enhancing the antihypertensive efficacy of ARBs; on the other hand, ARBs can offset thiazide-induced potassium loss [6].

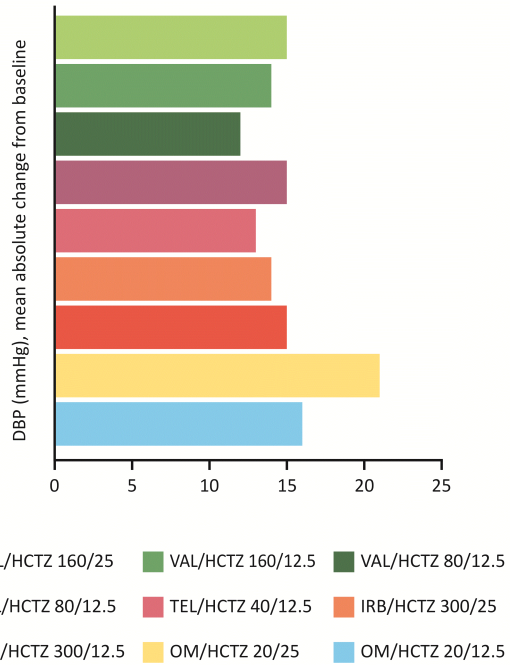


Figure 2: Change in diastolic blood pressure (DBP) from baseline, after 8 weeks of treatment, in hypertensive patients treated with different doses of olmesartan (OM), irbesartan (IRB), telmisartan (TEL), valsartan (VAL), all in combination with hydrochlorothiazide (HCTZ) 12.5 or 25 mg. Elaborated from (3).

Currently, there are some commercially available combinations of ARBs+thiazide diuretics, including the combination of olmesartan medoxomil (OM) and hydrochlorothiazide (HCTZ) [7].

OM reduces BP levels by blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin II, preventing its binding to its receptor subtype 1 (AT1). Animal and human studies have demonstrated that the prolonged antihypertensive effects of OM and the effects associated with RAS inhibition are due to a stable, insurmountable inhibition of the AT1 receptor by OM [4]. In hypertensive patients, OM produces sustained reductions in both systolic and diastolic blood pressure, in a dose-dependent manner, without first-dose hypotension, tachyphylaxis during extended treatment, or 'rebound hypertension' when treatment is discontinued [4]. The antihypertensive efficacy of the monotherapy with OM, administered once-daily, at all doses, compares favorably with that of other antihypertensive agents such as atenolol, captopril, felodipine and amlodipine besylate, as well as that of other ARBs, in clinical efficacy trials [4-6].

HCTZ is a thiazide diuretic commonly used in combination with other antihypertensive agents, including ARBs. The reflex activation of the renin-angiotensin-aldosterone system by HCTZ provides a strong rationale for the combination of this molecule with an ARB such as OM [6].

Clinical efficacy of OM/HCTZ combination

A search of the medical literature using MEDLINE and EMBASE (English-language articles only) was conducted using the keywords [olmesartan] AND [hydrochlorothiazide] AND [hypertension OR high blood pressure] AND [efficacy]. The full articles were retrieved and the results were then manually filtered to identify studies in which the efficacy of olmesartan/hydrochlorothiazide combination was evaluated in hypertensive patients, including "high-risk" patients subgroups, such as elderly and diabetic patients. Additional references were identified from the reference list of published articles. Searches were last updated on 31 December 2014.

Table 1 summarizes the study design, patients, interventions, and endpoints of the most relevant studies included in this review, in which blood pressure changes in patients treated with olmesartan medoxomil-based therapy were reported.

In some clinical studies, the efficacy of OM/HCTZ combination has been evaluated both in terms of reduction of office seated BP and 24-hour ambulatory monitoring (ABPM). In hypertensive patients, in fact, there is often a difference in efficacy outcomes when blood pressure reduction (obtained by treatment) is determined as office seated BP *vs* 24-hour ambulatory monitoring. For example, renal denervation has been shown to induce a marked reduction in office BP, which has been found to be sustained up to 3 years following the denervation procedure, but only limited reductions have been observed on 24-hour ambulatory BP [1].

In a randomized, double-blind, factorial design multicenter study, conducted by Chrysant et al. [6], the efficacy and safety of OM/HCTZ at various doses were evaluated *vs* placebo and monotherapy with either OM or HCTZ. After an initial single-blind, 4-week, placebo run-in period, eligible patients were randomized to 8 weeks of double-blind treatment with placebo, OM monotherapy (at doses of 10, 20, or 40 mg/day), HCTZ monotherapy (at doses of 12.5 or 25 mg/day), or OM/HCTZ combination therapy including all possible combinations of doses used in the monotherapy groups. A total of 502 patients were randomized to one of the 12 treatment groups (35/47 patients per group). All OM/HCTZ combinations significantly reduced both seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP) compared with placebo, in a dose-dependent manner. The mean SeSBP and SeDBP reductions from baseline for OM/HCTZ ranged from -20.5/-16.0 mmHg to -28.3/-22.3 mmHg. Reductions from baseline in mean trough SeSBP/SeDBP were -3.3/-8.2 mmHg, -20.1/-16.4 mmHg, and -26.8/-21.9 mmHg with placebo, OM/HCTZ 20/12.5 mg, and OM/HCTZ 40/25 mg, respectively.

The greatest reduction in SeDBP, about -22 mmHg, was observed in the group treated with the combination of OM/HCTZ 40/25 mg/day. Evidence of efficacy for all active treatments was observed as early as after 1 week of treatment, and increased throughout the course of the study. When analyzing responder rates (defined as trough SeDBP <90 mmHg or ≥ 10 mmHg reduction in SeDBP), these were found to increase after switching from OM to OM/HCTZ, progressively increasing with up-titration of OM/HCTZ to OM/HCTZ 40/25 mg/day (92.3%) (Figure 1).

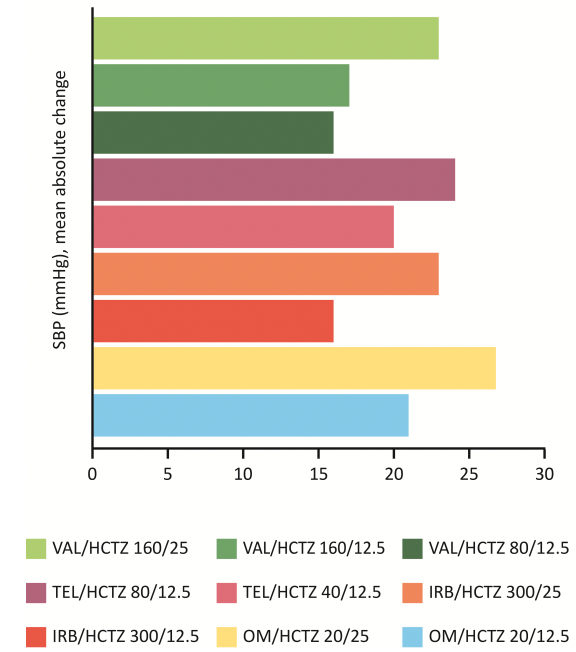


Figure 3: Change in systolic blood pressure (SBP) from baseline, after 8 weeks of treatment, in hypertensive patients treated with different doses of olmesartan (OM), irbesartan (IRB), telmisartan (TEL), valsartan (VAL), all in combination with hydrochlorothiazide (HCTZ) 12.5 or 25 mg. Elaborated from (3).

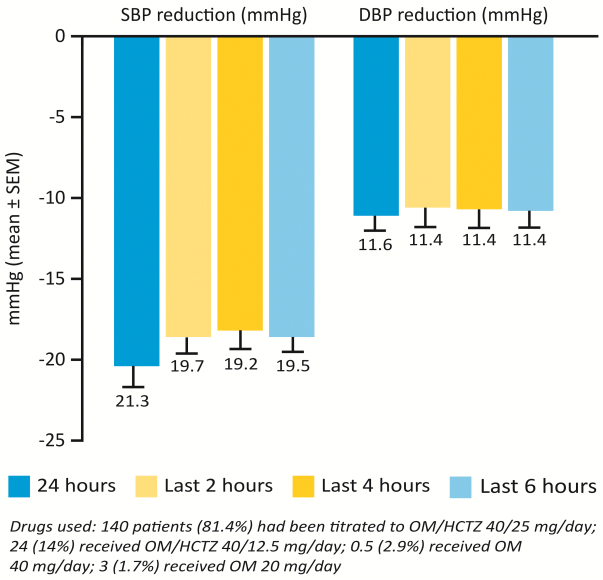


Figure 4: SBP and DBP reductions from baseline (mean ± SEM) over 24 hours, and in the last 2, 4, and 6 hours of the dosing interval in diabetic hypertensive patients treated with OM/HCTZ. Elaborated from (13).

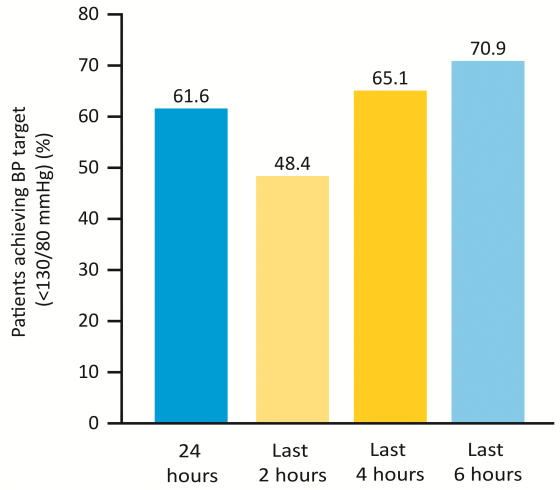
All doses of OM, either alone or in combination with HCTZ, were safe and well tolerated, and there were no significant or clinically relevant differences between different doses in the incidence of treatment-emergent adverse events (AEs) [7]. The combination of OM/HCTZ has demonstrated blood pressure changes and responder rates comparable to, and in some cases significantly higher than, other antihypertensive combinations.

A comparative review of four similarly designed factorial studies investigating the relative efficacy of 8 weeks of olmesartan, irbesartan, telmisartan or valsartan, each with or without HCTZ, showed that the magnitude of reductions in BP [both in DBP (Figure 2) and SBP (Figure 3)] was greater with the combination OM/HTCZ 20/25 mg/day than with any other combination of ARB/HCTZ [3].

Additional evidence for the efficacy of OM/HCTZ has been provided by a series of clinical studies included in a review by Punzi [8]. The BENIFORCE study, a 12-week, randomized, double-blind, placebo-controlled trial, was conducted in 276 patients with stage 1 or stage 2 hypertension [9]. After a run-in phase with placebo, patients were randomized to placebo (12 weeks) or to OM 20 mg/day (1-3 weeks). The OM-based treatment regimen was up-titrated in a stepwise fashion to OM 40 mg (4-6 week), OM/HCTZ 40/12.5 mg (7-9 weeks), and OM/HCTZ 40/25 mg (10-12 weeks) in patients whose BP remained >120/80 mmHg for each dosing interval.

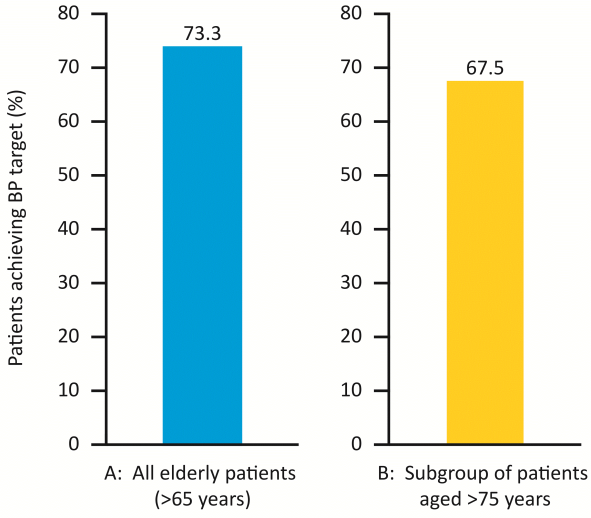
The OM-based treatment regimen produced significantly greater reductions in mean seated BP (SeBP) from baseline compared with placebo (22.3/12.1 mmHg *vs* 0.1/-0.8, p<0.0001). The cumulative percentage of patients achieving the BP goal of <140/90 mmHg was significantly higher with the OM-based treatment regimen compared with placebo (74.1% *vs* 30.7%, p<0.0001) [10]. In addition, a significantly greater percentage of patients treated with the OM-based regimen achieved BP normalization (<120/80 mmHg) compared with placebo (27.3% *vs* 1.5%; p<0.0001). Recently, a subgroup analysis of the BENIFORCE study indicated that the significant BP improvements achieved with OM/HCTZ treatment compared with placebo were independent of race, age, or sex [8-11].

A European study investigated the safety and tolerability of OM/HCTZ in 1226 patients with stage 2 hypertension [12]. Patients were initially treated with OM 40 mg/day during an 8-week open label phase. Patients who failed to achieve BP control (trough seated cuff SBP [SeSBP] of 140-180 mmHg and SeDBP of 90-115 mmHg, mean 24-hour DBP ≥ 80 mmHg and >30% of daytime DBP>85 mmHg) entered a randomized double-blind treatment phase of 8 weeks. In this phase, patients were randomized in a 2:2:2:1 scheme to OM 40 mg, OM/HCTZ 20/12.5 mg, OM/HCTZ 40/12.5 mg, and OM/HCTZ 40/25 mg. The primary endpoint was the change from baseline in SeDBP from week 8 to the end of week 16; with the highest dosage of OM/HCTZ (40/25 mg) the change in SeDBP was -11.2 mmHg compared with -5.7 mmHg in patients who remained on OM 40 mg monotherapy (p<0.0001). The change in SeSBP for the same time period was -16.2 mmHg for OM/HCTZ 40/25 mg compared with -8.9 mmHg for OM 40 mg (p<0.0001). The SeBP goal of <140/90 mmHg (<130/80 mmHg for patients with diabetes) was achieved by 42.1% of patients treated with OM/HCTZ 40/25 mg compared with 24.8% of those treated with OM 40 mg.



Drugs used: 140 patients (81.4%) had been titrated to OM/HCTZ 40/25 mg/day; 24 (14%) received OM/HCTZ 40/12.5 mg/day; 0.5 (2.9%) received OM 40 mg/day; 3 (1.7%) received OM 20 mg/day

Figure 5: Achievement rate of SBP and DBP targets as recommended by currently available ESC/ESH Guidelines (<130/80 mmHg) over the 24-hour period and in the last 2, 4, and 6 hours of the dosing interval in diabetic hypertensive patients treated with OM/HCTZ. Elaborated from (13).



Drugs used: OM 20 mg (n=176); OM 40 mg (n=169); OM/HCTZ 40/12.5 mg (n=159); OM/HCTZ 40/25 mg (n=125)

Figure 6: Achievement of 24-hour ambulatory PA target of <130/80 mmHg after 12 weeks of treatment, initiated with OM 20 mg and up-titrated to OM/HCTZ 40/25 mg in a stepwise manner, in all elderly patients (>65 years) (A) and in the subgroup of 'very old' patients (>75 years) (B), respectively. Elaborated from (8).

Use of OM/HCTZ combination in 'frail' hypertensive patients (diabetics, elderly patients)

Treatment with high-dose OM/HCTZ has been shown to be effective and well tolerated even in particularly 'frail' groups of hypertensive patients, such as patients with type 2 diabetes mellitus (T2DM) and the elderly, as discussed in a review by Punzi [8].

The BENIFICIARY study assessed 24-hour BP control in hypertensive patients with type 2 diabetes mellitus [13]. The patients enrolled in the study initiated treatment with OM 20 mg, up-titrated to OM 40 mg, OM/HCTZ 40/12.5 mg, and OM/HCTZ 40/25 mg if BP was <120/70 mmHg. Ambulatory blood pressure monitoring (ABPM) over 24 hours was performed at baseline and at the end of week 12. The primary endpoint was the change from baseline in mean 24-hour ambulatory SBP at week 12. At week 12, the reduction in 24-hour ambulatory BP was -20.4/-11.1 mmHg ($p<0.0001$ *vs* baseline), and ambulatory BP targets of <130/80, <125/75 and <120/80 mmHg were achieved by 61.6%, 47.1%, and 39.0% of patients, respectively. The use of OM/HCTZ was associated with a significant reduction in SBP and DBP from baseline throughout the 24-hour period and also during the last 2, 4 and 6 hours of the dosing interval (Figure 4), when the normal morning rise in BP occurs.

The SeBP reduction from baseline was -21.8/-9.9 mmHg in patients titrated to OM/HCTZ 40/25 mg intensified, and the majority of patients achieved the BP target recommended by currently available ESC/ESH Guidelines (<130/80 mmHg), both throughout the 24 hours and during the last hours of the dosing interval (Figure 5).

The efficacy and safety of OM/HCTZ combination in elderly patients were evaluated in the BeniSILVER study. This was a 12-week, open-label, multicenter trial, that enrolled a total of 178 elderly patients (>65 years) (8,14). Patients were initiated on OM 20 mg and up-titrated to OM/HCTZ 40/25 mg in a stepwise manner until pre-specified BP targets were achieved. The primary endpoint was the change in mean 24-hour ambulatory SBP from baseline to week 12.

At the end of the study, mean 24-hour ambulatory BP showed a reduction of -25.7/-12.3 mmHg from a mean baseline BP of 148.8/80.9 mmHg ($p<0.0001$ *vs* baseline). After 12 weeks, the mean 24-hour ambulatory BP target of <130/80 mmHg was achieved by 73.3% of patients.

BP control was maintained throughout the 24-hour dosing interval, with significant BP reductions from baseline observed during the last 6, 4 and 2 hours before the next dose ($p<0.0001$). A subgroup analysis in patients aged >75 years showed that 24-hour ambulatory BP target of <130/80 mmHg, <125/75, and <120/80 mmHg were achieved by 67.5%, 52.5%, and 40.0% of patients, respectively. These results demonstrate the efficacy of OM/HCTZ both in 'old' (>65 years) and in 'very old' (>75 years) hypertensive patients (Figure 6).

Further support for the efficacy of OM/HCTZ in diabetic and/or elderly hypertensive patients is provided by the results of the studies by Neutel [13], and by Kereiakes et al. [14], showing that as many as 70.9% of diabetic patients (24-hour ambulatory BP target <130/80 mmHg) and 88% of elderly patients (24-hour ambulatory BP target <140/80 mmHg) achieved BP targets during the last 'critical' six hours of the dosing interval as a result of treatment with OM/HCTZ (Figure 7).

Based on the results of BENIFICIARY and BeniSILVER studies, treatment with OM/HCTZ is effective in achieving and maintaining 24-hour BP control in various types of 'frail' hypertensive patients, including those with T2DM and the elderly [8,13,14].

Efficacy of OM/HCTZ combination in BP control over 24 hours

The 24-hour ambulatory blood pressure monitoring (ABPM) has been shown to be an important tool for the diagnosis of hypertension and for predicting the risk of CV events. Using ABPM measurements, studies have demonstrated that combination therapy with OM/HCTZ provides an effective BP control over 24 hours.

In a pooled analysis of two studies conducted by Rosenbaum et al. [7], the efficacy of combination therapy with OM/HCTZ on 24-hour BP control was compared with OM monotherapy in patients with moderate-to-severe hypertension. After 8-weeks of open-label treatment with OM 40 mg monotherapy, uncontrolled patients (mean trough seated BP 90-115/140-180 and 24-hour mean ambulatory diastolic BP ≥ 80 mmHg with ≥ 30% of daytime ambulatory diastolic BP readings ≥ 85 mmHg) were randomized to 8-weeks double-blind treatment with OM 40 mg or OM/HCTZ 20/12.5, 40/12.5 or 40/25 mg (Study 1) or OM/HCTZ 20/25 or 40/25 mg (Study 2).

The analysis of the treatment effects on ambulatory blood pressure was performed on those patients participating in these two studies, who provided at least one valid ABPM measurement at baseline. At baseline, the mean 24-hour ambulatory DBP and SBP profiles were similar in the OM 40 mg treatment group and in all OM/HCTZ treatment groups. However, at the end of the double-blind treatment period, patients not controlled by OM 40 mg monotherapy at baseline and who were subsequently randomized to OM/HCTZ (20/12.5, 20/25, 40/12.5 or 40/25 mg) combination therapy achieved greater mean reductions from baseline in their mean 24-hour ambulatory DBP and SBP profiles, compared with those patients who continued to receive OM 40 mg monotherapy.

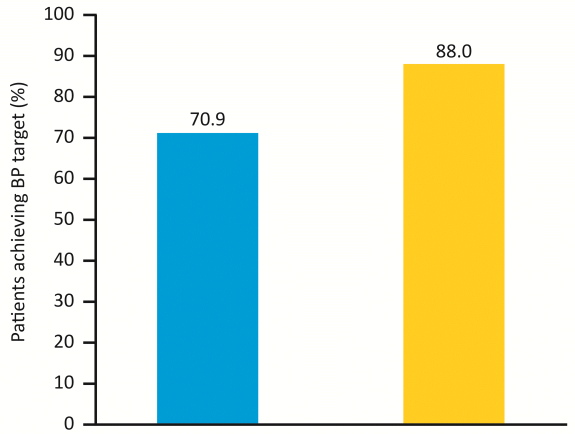
With regard to combination therapy, OM/HCTZ 40/25 mg was associated with the greatest reductions in 24-hour BP from baseline to week 16 compared with OM monotherapy (-14.0/-8.8 vs -2.7/-2.0 mmHg, respectively; $p<0.0001$).

In conclusion, the results of this analysis demonstrate that combination therapy with OM/HCTZ is associated with a more effective 24-hour BP control compared with OM monotherapy, and that the efficacy of BP control correlates linearly with the dose (the best results were observed with the highest dose of OM/HCTZ 40/25 mg).

Safety and tolerability of OM/HCTZ combination

A fixed-dose OM/ HCTZ combination is associated with an overall adverse event (AE) rate that is similar to placebo and to other ARB/ HCTZ combinations. AEs that occurred at a higher frequency than placebo in >2% of patients in OM/HCTZ trials include nausea, dizziness, upper respiratory tract infection, and hyperuricemia [8].

Further support to placebo-like tolerability of OM/HCTZ combination is provided by safety data in the BENIFORCE and in the BENIFICIARY trials [7,8].



[a]Drugs used: 140 patients (81.4%) had been titrated to OM/HCTZ 40/25 mg/day; 24 (14%) received OM/HCTZ 40/12.5 mg/day; 0.5 (2.9%) received OM 40 mg/day; 3 (1.7%) received OM 20 mg/day
[b]Drugs used: OM 20 mg (n=176); OM 40 mg (n=169); OM/HCTZ 40/12.5 mg (n=159); OM/HCTZ 40/25 mg (n=125)

Figure 7: Proportion of diabetic or elderly hypertensive patients achieving BP targets (24-hour ambulatory BP<130/80 mmHg and <140/80 mmHg, respectively) in the 'critical' last six hours of the dosing interval, as a result of treatment with OM/HCTZ. Elaborated from (13) and (14).

In the BENIFORCE study, for example, the incidence of at least one adverse event (AE) across titration steps during treatment with OM/HCTZ was similar to that observed during the run-in phase with placebo. In this study, the total number of treatment-related AEs was similar in the treatment group receiving OM/HCTZ (2.2%-7.6% across titration steps) and in the placebo group (2.1%-9.5%). The majority of AE were mild to moderate; the most common AE was dizziness (3.4%).

In elderly patients, dizziness and hypotension may be associated with relatively large BP reductions, especially in SBP. In the BeniSILVER study, conducted in elderly patients treated with OM/HCTZ, incidences of drug-related dizziness and hypotension were 3.4% and 2.2%, respectively.

In the BENIFICIARY study, conducted in hypertensive patients with T2DM, the incidences of drug-related AE (the most common of which were arthralgia and extremity pain) ranged from 0.5% to 7.6% across the titration steps.

The maximum dose of OM/HCTZ (40/25 mg) was not found to be associated with clinically significant decreases in sodium or potassium; glucose and uric acid levels, although slightly increased, were within normal limits and were not associated with clinically significant events [7,8].

OM/HCTZ is contraindicated in patients who are hypersensitive to any component of the combination; furthermore, because of the HCTZ component, this combination is contraindicated in patients with hypersensitivity to other sulfonamide-derived drugs. Other OM/HCTZ contraindications, according to its SMPC, include: refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia; severe renal impairment (creatinine clearance<30 ml/min); moderate or severe hepatic impairment, cholestasis and biliary obstructive disorders; women in the second or third trimester of pregnancy.

Discussion

As underlined by ESC/ESH Guidelines on arterial hypertension, monotherapy can effectively reduce BP in only a limited number of hypertensive patients; the greatest part of patients require the combination of at least two drugs to achieve BP control [1]. Improvement in BP control can be achieved by using antihypertensive drugs at full doses, improving therapeutic adherence, and using fixed-dose combinations. To reach the blood pressure targets recommended by ESC/ESH Guidelines, there is often the necessity of the combined use of drugs with different-yet complementary-modes of action. A typical example of rational antihypertensive combination therapy is given by the combination of an angiotensin II receptor blocker (ARB), such as olmesartan medoxomil, with a thiazide diuretic, such as hydrochlorothiazide (HCTZ).

A number of studies have shown that the combination of OM/HCTZ is an effective treatment option, having a good tolerability profile, and enabling a large percentage of patients to achieve the recommended BP target.

Combination therapy based on OM/HCTZ represents an effective and safe therapeutic option, providing greater blood pressure reduction than either of its components given as monotherapy; OM/HCTZ is particularly indicated in patients who fail to achieve BP targets using a single antihypertensive drug.

Treatment with OM/HCTZ (up to 40/25 mg/day), has been shown to be a rational approach to improve therapeutic efficacy and adherence in hypertensive patients; the simplicity of the dosage regimen (once daily), as well as its high efficacy and good tolerability, can improve treatment adherence and may have a positive impact in terms of outcomes [7].

In this respect, it should be noted that patient adherence to therapeutic regimens, especially in chronic diseases with a significant social impact, is a crucial factor that can also affect the prognosis. A higher adherence rate to antihypertensive medications has demonstrated a positive impact on blood pressure control, with benefits also in terms of reductions in the number of hospital admissions and overall healthcare costs. The efficacy and tolerability profiles, as well as the complexity of the therapeutic regimen, are the factors that most commonly affect the degree of adherence [15]. In this regard, a meta-analysis performed by Bangalore et al. [5] showed that fixed-dose combinations significantly reduced the risk of non-compliance by 26%, compared with free-drug combination regimens (when the components of the combination regimen are given separately) (pooled relative risk [RR] 0.74; 95% confidence interval [CI], from 0.69 to 0.80; p<0.0001).

OM/HCTZ combination is characterized by the ability to effectively control blood pressure throughout the 24 hours, thereby contributing to significantly reduce cardiovascular risk in hypertensive patients.

The efficacy of this combination has been demonstrated also in subgroups of particularly 'frail' patients, such as the elderly and diabetic patients. The availability of a wide range of doses and formulations makes it possible to individualize the dosage regimen for each hypertensive patient, in line with the recommendations of ESC/ESH Guidelines. Available evidence in the literature demonstrates

the good tolerability profile of OM+HCTZ, even at the highest doses (up to 40/25 mg/day).

To date, no large-scale intervention trials have specifically studied the efficacy of fixed-dose OM/HCTZ combinations on morbidity and mortality outcomes; however, the greater number of patients achieving blood pressure normalization when treated with OM/HCTZ, compared to monotherapy with either component, along with olmesartan's ability to induce a modest but significant regression of carotid [16] and coronary [17] atherosclerosis, further supports the extensive use of fixed-dose combinations in cardiovascular prevention.

Conclusions

The results of the clinical studies included in this review clearly demonstrate that combination therapy with olmesartan/hydrochlorothiazide (OM/HCTZ) shows a high clinical efficacy and a good safety profile (at doses up to 40/25 mg/day). The efficacy of this antihypertensive combination also extends to 'frail' patients such as the elderly (i.e. ≥ 65 years) and to patients with diabetes mellitus. In these populations, OM/HCTZ has been shown to be effective in achieving blood pressure targets in a large percentage of patients, and in maintaining a uniform blood pressure control throughout the dosing interval (24 hours).

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